This Month in *The Journal*

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Moving toward the Completion of the Human Reference Genome

Genovese et al., page 411

A map of the human genome is a valuable resource for the study of human genetics, and although we often think of the human genome as complete, in fact, there are many regions that are missing from the current reference sequence assembly. For example, the value of a reference sequence becomes readily apparent during attempts to characterize genes or loci that are missing from the human reference genome. These missing regions are often separated by heterochromatin and repeat-rich sequences, including those encoding centromeres, making them difficult to map with available sequencing technology. Admixture mapping in African Americans previously helped to place 4 Mbp of these complicated sequences in the genome, but a great deal of sequence remained unlocalized. In this issue, Genovese et al. use a three-way admixed population, Latinos, to localize an additional 20 Mbp of sequence. Latino genomes are uniquely suited for this task because in addition to the European and Native American polymorphisms, they contain the diverse African-ancestry polymorphisms that African Americans carry—but in limited amounts. In the future, this method could help researchers to localize the remaining missing sequence in forthcoming releases of the human reference genome, and the addition of these sequences will unveil regions that were previously inaccessible to scientists attempting to characterize genes that are encoded in these regions.

Extensive Cultural Mixing in India prior to the Caste System

Moorjani et al., page 422

India is known for, among other things, a diversity of people and culture, but there remain many mysteries surrounding the origins of this diversity. For example, although there is evidence for mixture between ancestral Indian populations, the date of this mixture has remained unknown. In this issue, Moorjani et al. evaluated 571 people from 71 different ethnic groups from both upper and lower castes in India and two groups from Pakistan to determine the extent of ancestral mixture in each group. Their analysis determined that a dramatic amount of intermarrying and mixture occurred between 1,900 and 4,200 years ago. By including various castes and geographic regions in the analysis, they determined that the mixture affected even considerably isolated tribes as well as both upper- and lower-caste groups. This finding contrasts with the present-day practice of marrying within a caste, suggesting that these endogamous practices have been relatively recently accepted as custom. Intriguingly, this estimated time of population mixture also corresponds to the collapse of the Indus civilization and the introduction of new languages and the Vedic religion, suggesting this was a time of immense change for the region. Although questions remain about the geographic region in which this mixture occurred, the narrowing of the time interval will allow future studies to focus on these additional details.

Not Suited for High-Altitude Living

Zhou et al., page 452

For those of us accustomed to life at or near sea level, a trip to the mountains can cause fatigue, dizziness, and nausea. By contrast, most high-altitude-dwelling populations are well adapted to the unique challenges posed by life in hypoxic conditions—their bodies can efficiently capture and transport limiting amounts of oxygen. But not everyone born into a high-altitude environment is so lucky; instead, some suffer from chronic mountain sickness (CMS), a disease typified by diverse neurological symptoms as well as blood thickening, which can lead to myocardial infarction or stroke. In this issue, Zhou et al. utilize whole-genome sequencing to identify the genetic underpinnings of CMS in Andean highlanders. Their work reveals a role for SENP1 and ANP32D in mediating a cellular response to hypoxia. Whereas SENP1 is a known erythropoiesis regulator, much less is known about ANP32D function. Previous work revealed that it has oncogenic properties, suggesting that it might play a key role in altering cellular metabolism in low-oxygen conditions. These findings not only shed light on the mechanisms underlying adaptation to high-altitude living, but they might also provide key insights into other pathological conditions, such as ischemia and cancer, in which hypoxia plays a contributing role.

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Schizophrenia Variants Might Predate European-African Divergence

Candia et al., page 463

Although rare variants are usually population specific, common variants can be identified across multiple populations. Additionally, common variants might collectively contribute to certain diseases such as schizophrenia. Taken together, one might suspect that common variants that contribute to disease in one population could also be identified and contribute to disease in a second population. Previous studies have looked for the overlap of significant variants from GWAS between populations or used a risk score approach. In a study in this issue, however, Candia et al. use a random-effects modeling approach by fitting all SNPs simultaneously to look at the amount of additive genetic variation that is shared between populations of European and African descent in schizophrenia. Because each SNP is treated as being independent, this method eliminates the need to estimate the individual SNP effect and prune SNPs for linkage disequilibrium. Using measures of genomic similarities at SNPs to estimate how correlated these SNPs are across populations, the authors show that between 50% and 75% of additive genetic variation underlying schizophrenia is shared between populations of European and African descent. This finding suggests that many of these SNPs tag schizophrenia-associated variants that might predate the divergence of European and African populations. Determining how these variants have remained in such diverse populations might reveal important characteristics about the biological dysfunction underlying schizophrenia.

No Longer an Orphan?

Bonnen et al., page 471; Gai et al., page 482

Mitochondria, as any textbook will attest, perform essential roles in powering the cell. It is not surprising, then, that many diseases, often ones that are severe and have an early onset, are caused by genetic defects that alter the function of these powerhouses. Although some pathogenic mtDNA mutations have been identified, many mitochondrial disorders are caused by mutations in nuclear genes that encode proteins whose cellular role is crucial to mitochondrial function. In this issue, Bonnen et al. and Gai et al. identify *FBXL4* mutations that cause encephalopathy in combination with lactic acidosis and other developmental abnormalities. Biochemically, this disorder is characterized by respiratory-chain defects and mtDNA depletion. FBXL4 belongs to the family of F-box proteins, best known for their role in phosphorylation-dependent ubiquitylation. To date, however, FBXL4 remains relatively uncharacterized. The results from both groups point to a role in mitochondrial quality control, but the identification of binding partners and substrates will be needed if the mechanism by which *FBXL4* mutations cause disease is to be fully elucidated.